

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-957

MEDICAL REVIEW(S)

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research**

DATE: 10/20/06

FROM: Joyce A Korvick, MD, MPH
DGP/ODE III

SUBJECT: Deputy Division Director Approval Comments
NDA 21-957

APPLICANT: AstraZeneca LLP

DRUG: Nexium® (esomeprazole magnesium)
for Delayed-Release Oral Suspension, 20 or 40 mg

DIVISION RECOMMENDATION:

The division review teams recommend approval of this NDA for the new Delayed-Release Oral Suspension of Nexium for the previously approved indications for the Delayed Release Capsules for both the 20 and 40 mg dose, based upon the demonstration of bioequivalence in study D9612C00032. I have reviewed this material and agree with the conclusions of the team.

I. Regulatory History:

Nexium (Delayed Release Capsules) is currently approved for the following indications:

- Reflux Disease (GERD): Healing of Erosive Esophagitis, Maintenance of Healing of Erosive Esophagitis, Symptomatic Gastroesophageal Reflux Disease
- Risk Reduction of NSAID – Associated Gastric Ulcer
- H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence
- Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome.

II. DISCIPLINE REVIEW SUMMARY AND COMMENTARY:

A. OPDRA/DDMAC/DMETS:

There were no safety concerns with this formulation. The DMETS consult was focused mainly on the package and carton labeling. These concerns were addressed in consultation with the CMC reviewers (this issue is outlined well in the MO TL review, the reader is referred to this review). Satisfactory resolution of the nomenclature was reached between the CMC

and Clinical Biopharmacology review groups, specifically the ordering of the wording "For Delayed-Release Suspension".

B. Chemistry and Manufacturing:

The reviewers recommended approval. It should be noted that while the sponsor submitted several different unit dosing of this formulation, the CMC review specifically only addresses the 20 and 40 mg dose. This is reflected in the labeling under the how supplied section.

C. Pre-Clinical Pharmacology/Toxicology:

There were no pharmacology/toxicology studies submitted for this package. This was found to be acceptable and appropriate by the reviewers based upon the chemical composition of this new formulation.

D. Biopharmaceutics:

A detailed review of "A Single-Center, Open, Randomized, Three-way Crossover Bioequivalence Study Comparing a Pellets Based Sachet Formulation of Esomeprazole with a Commercial Tablet and a Commercial Capsule of Esomeprazole 40 mg following a Single Oral Dose Under Fasting Conditions in Healthy Male and Female Subjects." The reviewer's conclusion was that the 40 mg sachet was bioequivalent to the currently approved and marketed capsule formulation. In addition the sponsor supplied dissolution profiles for _____ 20 mg and compared them to the 40 mg delayed release sachet. Based upon this data the sponsor requested a biowaiver for the 20-mg sachets. This was recommended by the reviewer. Therefore, the final recommendation was for approval of the 20 and 40 mg delayed release sachets.

E. Clinical/Statistical:

No new safety issues were raised by this application. The medial reviewer and team leader both recommended approval of this application.

F. Pediatric Use:

Currently there is an ongoing WR for GERD in pediatric patients. The other indications have been waived due to the small number of pediatric patients in those diseases.

III. Labeling Recommendations:

There were minor changes made in the proposed labeling during labeling negotiations, especially in the biopharm section of the labeling. These were agreeable to the sponsor. Please see the final labeling attached to the approval letter.

IV. Phase IV Commitments:

None are recommended.

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/s/

Joyce Korvick
10/20/2006 02:49:49 PM
MEDICAL OFFICER

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research**

DATE: October/05/2006

FROM: Hugo E. Gallo-Torres, MD, PhD, PNS
Medical Team Leader
Division of Gastroenterology Products
HFD-180/ODE III

SUBJECT: NDA 21-957
GI Team Leader AP Comments

NDA TYPE: 505(b) (2); submitted on December 22, 2005

NAME: Nexium® [Esomeprazole magnesium]

FORMULATION: Delayed-Release Oral Suspension
Dosing Regimen: 20mg and 40mg daily

THERAPEUTIC CLASS: Proton Pump Inhibitor

APPLICANT AstraZeneca LP
Regulatory Contact: George A. Kummeth, Director
Regulatory Affairs
Wilmington, DE 19803-8355

GI TEAM RECOMMENDATION ON REGULATORY ACTION

The sponsor submitted results of one study [D9612C00032] demonstrating the bioequivalence of a pellet-based sachet formulation of esomeprazole to the tablet (not available in the US) and delayed-release capsule. The sachet formulation is aimed as an alternative to the capsule formulation for all currently approved indications of NEXIUM. No new safety issues were identified during the multidisciplinary review and evaluation of the evidence.

Approval of this application for Nexium® (Esomeprazole Magnesium) delayed release oral suspension is recommended. All disciplines involved with the review of the pertinent sections of this application are in agreement with the approval recommendation for regulatory action.

The pellet-based sachet formulation¹ is a new formulation of esomeprazole that can be administered orally (for example by drinking and syringe) or by administration via nasogastric and gastric tubes. This new formulation is intended for all patients who have difficulty swallowing a capsule, such as a) patients that have esophageal structural anomalies (esophageal strictures, and diverticuli), b) those with esophageal dysmotility characterized by dysphagia, or c) those with functional swallowing disorders. Additional potential users of the sachet formulation include geriatric and pediatric patients, and those who receive nutrition and medication through feeding tubes. Lastly, there are patients who simply prefer or require an alternative to a solid drug formulation.

- The sachet formulation of esomeprazole is being developed as strengths: 20, and 40 mg; however only 20 mg and 40 mg strengths are subject to approval in this application. The proposed changes to the Package Insert for NEXIUM will provide information on the sachet alternative administration option for the currently approved capsule indications (the 20 and 40 mg strengths only).

I. BACKGROUND

NEXIUM® [esomeprazole], the S-enantiomer of omeprazole, is a proton pump inhibitor [PPI] approved for the treatment of a variety of conditions where effective inhibition of gastric acid secretion is needed. In the United States, these approved indications include the short-term treatment of symptomatic gastroesophageal reflux disease [GERD], the short-term treatment of erosive esophagitis, maintenance of healing of erosive esophagitis, and risk reduction of NSAID-associated gastric ulcer. In addition, NEXIUM® is indicated in combination with an appropriate antibacterial therapeutic regimen for the eradication of *Helicobacter pylori* infection in patients with duodenal ulcer disease.

In the United States, NEXIUM® is available as Delayed-Release Capsules. NEXIUM® has also been formulated as tablet, but this form of the drug is not available in the United States.

The current application is being submitted to support the use of an oral suspension as a new dosage form of esomeprazole [pellet-based sachet]. The rationale for the pellet-based sachet formulation is to provide esomeprazole to patients who have difficulty swallowing a capsule, such as those patients with esophageal structural anomalies, those with esophageal dysmotility and dysphasia, geriatric patients, and those receiving nutrition and medication through feeding tubes. The indications for the pellet-based sachet formulation will be the same: [all] indications currently approved in the U.S. under NDA 21-153 [NEXIUM® delayed-release capsules].

¹ The sachet formulation consists of the same enteric-coated pellets of esomeprazole as the capsule formulation. Besides these acid-stable pellets, the sachet formulation contains inactive excipient granules. The contents of the sachet are to be mixed with water and the suspension can be left for up to 30 minutes before administration.

In support of the current application, the sponsor submitted results of an open-label, randomized, 3-way crossover study [D9612C00032]. The aim of this single trial was to show bioequivalence between the approved oral formulations [tablet, and delayed-release capsule] and the proposed pellet-based sachet formulation. The study enrolled 96 healthy subjects, 20 to 50 years of age.

II. DISCIPLINE REVIEW SUMMARY AND COMMENTARY

A. DDMAC

On September 26, 2006, Michael Brony, the DDMAC reviewer, recommended the following:

In the Information for Patients section, there is discussion of the administration options. DDMAC recommend cross referencing this section with the Dosage and Administration section by including the following statement: "(see Dosage And Administration)."

B. DMETS

Listed below, are Dr. Kristina C. Arnwine's recommendations. These were included on her September 22, 2006 review of NDA#: 21-957.

1. DMETS has no objections to the use of the proprietary name, Nexium. This is considered a final decision. If the approval of the NDA is delayed beyond 90 days from the signature date of this document, the name with its associated labels and labeling must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in section IV of this review to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name, Nexium Delayed-release Oral Suspension, acceptable from a promotional perspective. DMETS would appreciate feedback of the final outcome of this consult. They would be willing to meet with the Division for further discussion, if needed.

NOTE: Section IV of the DMETS consult review is excerpted below, for completeness.

IV. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Nexium Delayed-release Granules for Oral Suspension, DMETS has focused on safety issues relating to possible medication errors. DMETS has identified the following areas of improvement, which will minimize potential user error.

A. General Comments

1. DMETS notes that the strength is based on the active moiety. Thus, we suggest revising the labels and labeling in one of the three following formats. Please note that DMETS prefers choice 'a' because this nomenclature is consistent with USP recommendations on "amount of ingredient

per dosage unit”.

a. Nexium
(Esomeprazole Delayed-release [redacted] Oral Suspension)
XX mg

b. Nexium
(Esomeprazole Magnesium Delayed-release [redacted] Oral Suspension)
XX mg*

*Each packet contains esomeprazole magnesium equivalent to XX mg of esomeprazole

c. Nexium
(Esomeprazole Magnesium Delayed-release [redacted] Oral Suspension)
equivalent to XX mg esomeprazole

2. Indicate specifically how long “a few minutes” is with regard to how long a patient must wait for the suspension to thicken.

B. Packet Label (20 mg and 40 mg, trade packet)

1. See General Comments A-1 and A-2.

2. The color schemes used for the 20 mg and 40 mg capsules are identical (gray background with black text). A lack of distinct differentiation between the product strengths may lead to selection errors, especially if the packets are not stored in the cartons. Revise so that the strengths are differentiated using methods such as boxing, differing color schemes, etc.

3. The graphic presented immediately above the proprietary name and in the bottom right corner of the packet distracts from and decreases the readability and prominence of important information such as the proprietary and established names, as well as the product strengths (see page 6). Decrease the prominence of these graphics.

4. Clarify or remove the statement, “Opening Instruction.” As currently presented there are no instructions regarding the opening of the packet (see page 6). If the intent of this statement is to clue patients in on how to open the packet, the language should be revised so that it provides instructions to the patient such as “cut here” or “open here”.

C. Packet Label (20 mg and 40 mg, Physician’s Sample)

1. See General Comments A-1 and A-2 and comments B-2 through B-4.

2. Increase the prominence of the statement, “Physician’s Sample – Not For Sale.”
Comment B-3: Decrease the prominence of these graphics

Comment B-4: Clarify or remove this statement.

Comment C-2: Increase the prominence of this statement.

D. Carton Labeling (20 mg and 40 mg, 30 count)

1. See General Comments A-1 and A-2.

2. The color schemes used for the 20 mg capsules and 40 mg capsules (purple background with white text) are identical, with exception to the background color used for the product strength (blue background with white font for 20 mg vs. white background with purple font for 40 mg). A lack of distinct differentiation between the product strengths may lead to selection errors.

DMETS recommends increasing the size of the strength in order to increase its prominence against the purple background which overwhelmingly causes the cartons to look similar. Additionally, we request a different background color be used for each strength to avert potential product selection errors.

E. Carton Labeling (20 mg and 40 mg, Physician's Sample)

See General Comments A-1 and A-2 and comments C-2 and D-2.

F. Insert Labeling

1. See General Comment A-1.

2. Remove the trailing zeroes used throughout the package insert (e.g. Precautions Section, Carcinogenesis, Mutagenesis, Impairment of Fertility Subsection and Pregnancy Subsection). The use of trailing zeroes is specifically listed as a dangerous abbreviation, acronym, or symbol. The FDA in conjunction with the ISMP launched a campaign on June 14, 2006 to reduce medication mistakes and/or confusion caused by unclear medical abbreviations. Thus in order to comply with these recommendations, we request all trailing zeroes be removed from the insert.

3. Precautions, Information for Patients Sub-Section

See comment A-2.

4. Dosage and Administration Section, Administration Options Subsection

a. See General Comment A-2.

b. Nexium Delayed-Release Capsules Subsection

C. CHEMISTRY AND MANUFACTURING

a. Summary of Chemistry Assessments

In his Chemistry review, Milton J Sloan, PhD [ONDQA pre-Marketing Assessment Division II Branch IV] provides a) a description of the Drug Substance and the Drug Product; b) a description of how the Drug product is intended to be used; c) the basis for approvability and d) Recommendations. Only salient points are highlighted below.

The drug substances, esomeprazole magnesium trihydrate, as well as the esomeprazole pellets were originally approved for the NEXIUM (esomeprazole magnesium) Delayed-Release Capsules NDA 21-153. The information on the drug substance is not included in the current NDA, but has been taken from the cross-referenced capsules NDA mentioned above and included in Dr. Sloan's review. Regarding the Drug Products, Dr. Sloan notes that Esomeprazole contains esomeprazole pellets and excipient granules, which are both filled into single-use, child resistant, aluminum packet (denoted as sachet by the sponsor). Although information has been included in the NDA for 20, and 40mg, in the original NDA submission, the currently proposed and approved indications and dosages of NEXIUM only encompass the 20 and 40 mg strengths². The full contents of a single sachet are added to water 15mL for the 20, and 40 mg strengths of esomeprazole) to form a viscous suspension, which can be left for up to 30 min before administration.

The proposed clinical use is as an alternative "Sachet formulation" to NEXIUM[®] Delayed-Release Capsules³.

The basis for approvability is the demonstrated bioequivalence between the 40 mg of the proposed dosage form and 40mg of NEXIUM[®] Delayed Release Capsules [Clinical study Report D9612C00032]. According to the CMC reviewer, a waiver of bioequivalence studies for the strengths lower than 40 mg is justified based on dose proportionality⁴.

b. Chemistry Reviewer's Recommendations

1. The application is recommended for approval from the CMC perspective.
2. There are no recommendations on PM Commitments, Agreements and/or Risk Management Steps.
3. List of comments to be communicated:

Labeling and Nomenclature Comments

The following nomenclature is recommended:

Nexium[®] (esomeprazole magnesium*) for Delayed-release Oral Suspension.

²NEXIUM has been on the market as an oral formulation at the doses of 20 and 40 mg since the year 2000, and as an I.V. formulation at the same dosage since 2003. The three lower strengths are intended to facilitate administration to pediatric populations, subject to future submissions.

³This newly proposed dosage form of esomeprazole is for an orally suspended drug product that is suitable for administration by spoon, drinking or through an enteric tube.

⁴The sponsor has demonstrated that the esomeprazole pellets are the same as the enteric coated esomeprazole pellets that are used in the approved capsule formulation.

*This packet contains 22.3 mg of esomeprazole magnesium trihydrate which is equivalent to 20 mg of esomeprazole as enteric-coated granules.

The term pellet may be acceptable in regards to the capsule dosage form however, it is not recommend for use with the for delayed-release oral suspension dosage form.

Other changes have been made to the annotated draft label under track changes. The edits to the document are not global but only as example.

Expiration:

The recommended expiry date for this drug product is ~~12~~ months.

Other Comments

The CMC reviewer alluded to the possibility of considering comments from DMETS consult review.

D. PRE-CLINICAL PHAMACOLOGY/TOXICOLOGY

NDA 21-957 included no new animal Pharmacology/Toxicology studies.

Since the drug substance [esomeprazole Mg] and the esomeprazole pellets in the sachet formulation are considered identical to those used in the currently approved NEXIUM Delayed-Release Capsules, the existing nonclinical documentation supporting the oral use of esomeprazole is considered to be relevant for both formulations of NEXIUM⁵. No additional nonclinical studies are considered necessary to specifically support the use of the sachet formulation.

E. DSI

No DSI inspections were required or requested.

F. CLINICAL PHARMACOLOGY

The Clinical Pharmacology reviewer of this application was Tapash K Ghosh, PhD. What follows are excerpts from his review. Only salient points are highlighted.

a. Overview of Clinical Pharmacology Program

The clinical pharmacology of esomeprazole administered as capsule was presented in the original application for NEXIUM (NDA (NDA 21-153) Capsule. As bioequivalence was established between the capsule formulation and the new sachet formulation of esomeprazole, these pharmacodynamic and pharmacokinetic data were applied to the current application as well.

⁵ The drug substance, esomeprazole Mg trihydrate, as well as the as esomeprazole pellet composition were originally approved in the NEXIUM [esomeprazole Mg] Delayed-Release Capsules NDA 21-153, in February 2001.

b. Dosage Form Description

[See also CMC and Clinical/Statistical Sections of the current review]

The composition of the 20 and 40 mg strengths of esomeprazole Sachets is presented in Table 1.

**Table 1
NDA 21-957
Composition of Esomeprazole Sachets**

COMPONENTS	Quantity (mg/sachet)	
	20	40
ESOMEPRAZOLE PELLETS		
Esomeprazole	20	40
Glycerol monostearate 40-55		
Hydroxypropyl cellulose		
Magnesium stearate		
Methacrylic copolymer type C		
Polysorbate 80		
Sugar spheres,		
Talc		
Triethyl citrate		
WEIGHT OF ESOMEPRAZOLE PELLETS		
EXCIPIENT GRANULES		
Xanthan gum		
Citric acid		
Iron oxide,		
Hydroxypropyl cellulose		
WEIGHT OF EXCIPIENT GRANULES		
TOTAL WEIGHT IN SACHET		

c. Summary Review of Study D9612C00032

"A Single-Centre, Open, Randomized, Three-way Crossover Bioequivalence Study Comparing a Pellets Based Sachet Formulation of Esomeprazole with a Commercial Tablet and a Commercial Capsule of

Esomeprazole 40mg following a Single Oral Dose under Fasting Conditions in Healthy Male and Female Subjects

- The primary objective of this study was to investigate whether a new pellets based sachet formulation of esomeprazole is bioequivalent to a commercial tablet and a commercial capsule of esomeprazole following single oral doses of 40 mg, respectively, by assessment of 1) the total area under the plasma concentration versus time curve (AUC); and 2) the observed maximum plasma concentration (C_{max}).
- The secondary objectives to evaluate the PK properties of a new pellets based sachet formulation of esomeprazole, a commercial tablet, and a commercial capsule of esomeprazole following single oral doses of 40 mg, respectively, by assessment of three PK parameters: 1) the area under the plasma concentration versus time curve up to the last quantifiable concentration (AUC_t); 2) the time of observed maximum plasma concentration (t_{max}); and c) the plasma terminal half-life ($t_{1/2}$).
- To evaluate the safety and tolerability of treatment with single doses of a pellets based sachet formulation of esomeprazole in relation to a commercial tablet and a commercial capsule of esomeprazole by assessment of adverse events (AEs) and laboratory variables.
- The trial was conducted as a single-centre, open-label, randomized, 3-way crossover bioequivalence study in which healthy male and female volunteers. Single oral doses of esomeprazole 40 mg were given either as a tablet, a capsule, or a pellets based sachet formulation⁶.
- 96 healthy M and F subjects, aged between 20 and 50 years inclusively, with ca. 50% of each sex, were included in the study in order to have at least 88 evaluable healthy subjects completing the study. In total, 122 subjects were enrolled in this study. Ninety-six (96) subjects (40 males and 56 females) were planned for and randomized into the study. All 96 subjects completed the study. Two (2) subjects were excluded from the statistical PP analysis because of major protocol deviations. Ninety-four (94) of the randomized subjects were thus included in the statistical evaluation of the pharmacokinetic variables. All 96 randomized subjects were included in the safety analysis.
- For the PK variables AUC, C_{max} , and AUC_t, a mixed model analysis of variance (ANOVA) with fixed effects for period, sequence, and treatment (sachet formulation, tablet, or capsule of esomeprazole) was used⁷. Data from subjects with major protocol deviations were excluded from the statistical evaluation. Subjects with PK data available from only 1 study day were also excluded from the statistical analysis and missing values were not replaced. Analyses and the evaluation of safety were done in the safety population, defined as all subjects who received at least 1 dose of randomized treatment.

⁶ Batch numbers were: H 1365-01-03-08 for the tablet, H 1222-06-07-02 for the capsule, and H 1784-01-01-01 for the sachet formulation.

⁷ The results were anti-logarithmized and 2-sided 90% CIs for the ratio of geometric means for the formulations (sachet/tablet and sachet/capsule) were calculated. The remaining secondary variables, t_{max} and $t_{1/2}$, are presented with descriptive statistics. A Per Protocol (PP) approach was used for the statistical analysis.

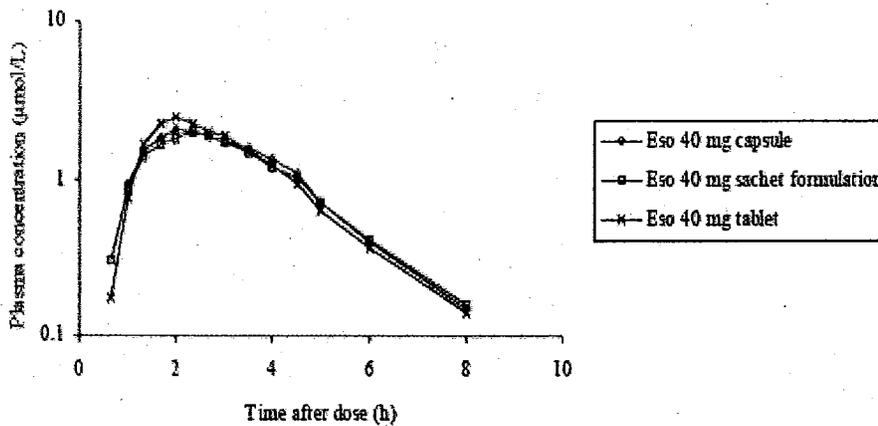
with the investigational products and for whom post-dose data are available [see Clinical Section of the current review].

- Drug concentration measurements were adequate.

Succinct Summary of Results [from Clinical Pharmacology review]

Dr. Ghosh explains that although the sponsor conducted this study as a 3-arm crossover design with the proposed Sachet formulation, tablets and capsules, data pertaining to tablets were not reviewed because esomeprazole tablets are not approved in the US. For the purpose of determining BE, data from sachet were reviewed against data from capsules only.

- Mean plasma concentrations, log scale, of esomeprazole following single oral doses of 40 mg given as a sachet formulation, a tablet and a capsule in healthy M and F subjects under fasting conditions is shown in Figure 1, below.



- The estimated **geometric means** and 95% CIs for AUC, C_{max}, and AUC_t for the sachet formulation, and the capsule of esomeprazole 40 mg, following single oral dosing, are summarized in Table 2.

Table 2
NDA 21-957

Estimated geometric means of the pharmacokinetic variables in healthy male and female subjects under fasting conditions
n = 94 in each and all Study arms

VARIABLE	TREATMENT	ESTIMATE
AUC (µmol*h/L)	Sachet	5.85
	Capsule	5.97
C _{max} (µmol/L)	Sachet	2.84

	Capsule	3.16
AUC _t (μmol*h/L)	Sachet	5.73
	Capsule	5.85

- The estimated ratios of the geometric means (sachet/tablet and sachet/capsule) and 90% CIs for AUC, C_{max}, and AUC_t following single oral doses of esomeprazole 40 mg, are summarized in Table 3. In this Table, the Clinical Pharmacology reviewer listed the secondary variable AUC_t together with the primary variables. This approach gives an additional comparison of the systemic exposure between the different formulations. As shown in Table 3, the 90% CIs for the ratios of the geometric means (sachet/capsule) of AUC and C_{max} were within the interval of 0.80 to 1.25, **which is the stated criterion for bioequivalence**. The 90% CIs for the ratios of the geometric means (sachet/capsule) of AUC_t were also within the interval of 0.80 to 1.25. The mean of t_{1/2} was ca. 1.1 h and the median of t_{max} was 2.0 h for both formulations is depicted in Table 4.

Table 3
NDA 21-957

Ratios (sachet/capsule) of geometric means and 90% CIs for AUC, C_{max} and AUC_t following single oral doses of esomeprazole 40 mg in healthy male and female subjects under fasting conditions

VARIABLE	TREATMENT	n	GMR	90% CI	
				Lower	Upper
AUC(μmol*h/L)	Sachet/Capsule	94	0.98	0.93	1.03
C _{max} (μmol/L)	Sachet/Capsule	94	0.90	0.84	0.96
AUC _t (μmol*h/L)	Sachet/Capsule	94	0.98	0.93	1.03

Table 4
NDA 21-957

Descriptive statistics of t_{1/2} (h) and t_{max} (h) following single oral doses of esomeprazole 40 mg given as a sachet formulation, and a capsule in healthy male and female subjects under fasting conditions

VARIABLE	n	TREATMENT	
		Sachet	Capsule
t _{1/2} (h) ± SD	94	1.09 ± 0.46	1.07 ± 0.39
t _{max} (h) ± SD	94	2.32 ± 0.94	2.18 ± 1.01

d. Clinical Pharmacology Reviewer's Conclusions

- The 90% CIs for the ratios (sachet/capsule) of the geometric means for AUC, AUC_t and C_{max} were contained in the interval 0.80 to 1.25, and thus the new pellets based sachet

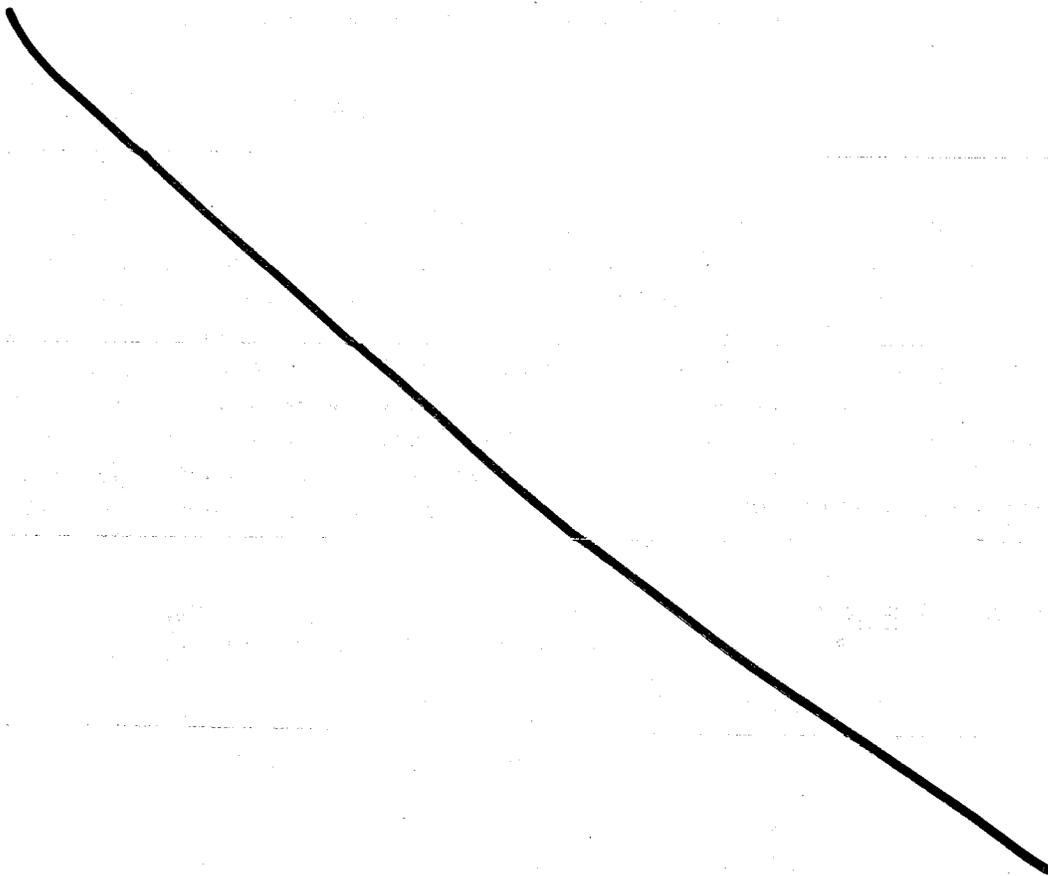
formulation of esomeprazole is considered to be bioequivalent to the commercial capsule of esomeprazole 40 mg.

- Esomeprazole 40 mg given as a sachet formulation resulted in similar values of t_{max} and $t_{1/2}$ as when given as a capsule.
- According to the sponsor, all 3 formulations of esomeprazole were well tolerated in this study. There were no findings that raised any safety concerns.
- The reviewer's analysis of BE data between the sachet and capsule formulations are in agreement with the sponsor's result.

e. Clinical pharmacology Reviewer's Recommendations

1. The Clinical Pharmacology and Biopharmaceutics section of NDA 21-957 is acceptable with the suggested labeling changes and dissolution specification as described below.

2. **Proposed CP LABELING Recommendations**



3. Proposed Dissolution Recommendation

Not less than \dots % (Q) of label claim of Esomeprazole released at pH 6.8 buffer preceded by exposure of the drug product to 0.1 M hydrochloric acid for 2 h using a USP apparatus 2 (paddle at 100 rpm, 37°C).

G. CLINICAL/STATISTICAL

As previously noted, the current application is for the oral suspension, to be used as an alternative to the capsule formulation for all currently approved indications of esomeprazole. The application is supported by results of Study D9612C00032, a bioequivalence study, assessed by the Division of Clinical Pharmacology [see above]. No clinical endpoints were evaluated. Efficacy was based on establishing bioequivalence between 40 mg of the proposed pellets based sachet formulation and 40 mg of the approved Delayed-Release granules formulation available in the U.S. In this bioequivalence study, a third arm [Tablet formulation] was included, but the results from this third arm were not considered because this formulation is not available in the U.S. The clinical reviewer was Dr. Nancy Snow. Only salient points from her review are noted below.

- The primary PK objective [assessment of bioequivalence through analysis of AUC and C_{max}] and the secondary PK objectives [assessment of bioequivalence through analysis of AUC_t, t_{max}, and t_{1/2}; and evaluation of the safety of the three formulations] were adequate for this type of study.
- As summarized in the Clinical Pharmacology Section of the current review the PK parameters of evaluation demonstrated bioequivalence between the proposed pellets based Sachet and the Delayed-Released capsule formulations.

One of Dr. Snow's conclusions was that the safety data submitted for bioequivalence study D9612C00032 did not raise new safety concerns. All 3 formulations tested [Delayed-Release Suspension, Delayed-Release Capsule, and Tablet] of esomeprazole were well tolerated in this study. No trends of clinical importance were found regarding AEs in relation to the different formulations of investigational product. There were no pregnancies, no serious adverse events (SAEs), no deaths, and no discontinuations of investigational product due to AEs. No subject had a significant laboratory abnormality.

- No new drug interactions were noted in this study. The current labeling provides details concerning drug interactions and notes extensive metabolism in the liver by CYP2C9 and CYP3A4.
- With regards to Special Populations, the current labeling for esomeprazole indicates no dosage adjustment based on age or gender is necessary. Additionally, no dosage adjustment is recommended for patients with mild to moderate hepatic insufficiency, nor

are the PKs of esomeprazole in patients with renal impairment altered relative to those without renal impairment.

- Further details on safety, including the most commonly reported AEs [headache, pharyngitis, nausea, and rhinitis, which were spread out evenly among all three treatment arms] are given in Dr. Snow's Medical Officer's review.

III. OVERALL SUMMARY

Esomeprazole magnesium is a proton pump inhibitor used in the treatment of acid-related disorders approved for both oral and intravenous administration. Oral dosage includes Delayed-Released Capsules [available in the U.S.] and Delayed-Released Tablets [not available in the U.S.]. The current application provides documentation in support of the use of a pellet based Sachet formulation of esomeprazole as a new oral dosage form of esomeprazole. The Sachet formulation is proposed as an alternative to the capsule formulation for all currently approved indications of NEXIUM[®]. The NEXIUM[®] sachet clinical development program was limited to Study D9612C00032, with the primary objective of showing bioequivalence between the new pellet based sachet and the capsule formulations.

- The clinical efficacy of esomeprazole administered as capsule was presented in the original application for NEXIUM (NDA 21-153). Efficacy data on the new sachet formulation are not considered necessary due to the established bioequivalence between the capsule and sachet formulations. The previously submitted efficacy data for esomeprazole are considered to be applicable to the current application as well.
- Detailed review of the evidence, carried out by Dr. T K Ghosh [OCPB Division, DCP III, HFD-880] demonstrated that the 90% CI for the ratios (sachet/capsule) of the geometric means for AUC, AUC_t and C_{max} were contained in the interval 0.80 to 1.25. Therefore, the new pellets based sachet formulation of esomeprazole is considered to be **bioequivalent** to the commercial capsule of esomeprazole 40mg. The CP reviewer's analysis of BE data between the sachet and capsule formulations were in agreement with the sponsor's results. Dr. Ghosh found the CP and B section of NDA 21-957 acceptable.
- Finally, the purpose of safety assessments in this application was to compare the safety profile of esomeprazole administered via the new sachet formulation and the well-characterized capsule formulation. Since its launch in August 2000, the total worldwide exposure to esomeprazole as oral NEXIUM has been estimated to be approximately patient treatment courses (as of 30 September 2005). Previous experience, both from clinical trials and from clinical practice, has shown an excellent safety profile for esomeprazole, consistent with that of other PPIs.

IV. LABELING RECOMMENDATIONS

A. Sponsor's proposed labeling

39 Page(s) Withheld

 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process

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/s/

Hugo Gallo Torres

10/13/2006 06:54:00 PM

MEDICAL OFFICER

Secondary Review of NDA 21-957 [NEXIUM Delayed-Release Granules for
Oral Suspension]

**Division of Gastroenterology Products
Clinical Review**

Application Type NDA/21-957

Submission Date 12/22/05

PDUFA Goal Date 10/22/06

Name Nexium® Esomeprazole magnesium
Therapeutic Class Proton Pump Inhibitor

Applicant AstraZeneca
Regulatory Contact George A. Kummeth, Director
Regulatory Affairs
Wilmington, DE 19803-8355

Priority Designation S
Formulation Delayed Release Granules for Oral
Suspension
Dosing Regimen 20mg & 40mg daily

Indication Acute Healing and Maintenance
Erosive Esophagitis, Symptomatic
GERD, Risk reduction of NSAID-
Associated Gastric Ulcer

Reviewer Dr. Nancy F. Snow
Medical Officer
HFD-180

Table of Contents

1	EXECUTIVE SUMMARY	4
1.1	RECOMMENDATION ON REGULATORY ACTION	4
1.2	RECOMMENDATION ON POSTMARKETING ACTIONS	4
1.2.1	Risk Management Activity	4
1.2.2	Required Phase 4 Commitments	4
1.3	SUMMARY OF CLINICAL FINDINGS	4
1.3.1	Brief Overview of Clinical Program	4
1.3.2	Efficacy	5
1.3.3	Safety	5
1.3.4	Dosing Regimen and Administration	5
1.3.5	Drug-Drug Interactions	6
1.3.6	Special Populations	6
2	INTRODUCTION AND BACKGROUND	7
2.1	PRODUCT INFORMATION	7
2.2	CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS	7
2.3	AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES	8
2.4	IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS	8
3	SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES	8
3.1	CMC (AND PRODUCT MICROBIOLOGY, IF APPLICABLE)	8
3.2	ANIMAL PHARMACOLOGY/TOXICOLOGY	8
3.3	DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY	8
3.4	SOURCES OF CLINICAL DATA	8
3.5	COMPLIANCE WITH GOOD CLINICAL PRACTICES	9
3.6	FINANCIAL DISCLOSURES	9
4	CLINICAL PHARMACOLOGY	9
4.1	PHARMACOKINETICS	9
5	INTEGRATED REVIEW OF EFFICACY	9
5.1	INDICATION	10
5.1.1	General Discussion of Endpoints	10
5.1.2	Study Design	10
5.1.3	Efficacy Findings	12
5.1.4	Efficacy Conclusions	12
6	INTEGRATED REVIEW OF SAFETY	13
6.1	METHODS AND FINDINGS	13
6.2	DEATHS	13
6.2.1	Other Serious Adverse Events	13
6.2.2	Dropouts and Other Significant Adverse Events	13
6.2.3	Common Adverse Events	13
6.2.4	Laboratory Findings	15
6.2.5	Vital Signs	15
6.2.6	Electrocardiograms (ECGs)	15
6.3	ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS	15
6.3.1	Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety	15
6.3.2	Study type and design/patient enumeration	15

Clinical Review
Nancy F. Snow
NDA21-957
Nexium® Esomeprazole magnesium pellets

6.4	SUMMARY OF SELECTED DRUG-RELATED ADVERSE EVENTS, IMPORTANT LIMITATIONS OF DATA, AND CONCLUSIONS	16
7	ADDITIONAL CLINICAL ISSUES	16
7.1	DOSING REGIMEN AND ADMINISTRATION	16
8	OVERALL ASSESSMENT.....	16
8.1	CONCLUSIONS	16
8.2	RECOMMENDATION ON REGULATORY ACTION	17
8.3	LABELING REVIEW	17

1. EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Approval of this application for Nexium® (Esomeprazole Magnesium) delayed release granules for oral suspension is recommended. The sponsor has submitted one study demonstrating the bioequivalence of a pellet-based sachet formulation of esomeprazole to the tablet and delayed-release capsule. No new safety issues were identified.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

From a clinical perspective, risk management activity is not recommended.

1.2.2 Required Phase 4 Commitments

From a clinical perspective, Phase 4 commitments are not recommended.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The current application is being submitted to support the use of an oral suspension as a new dosage form of esomeprazole. Esomeprazole is a proton pump inhibitor that is currently approved for the following indications; symptomatic treatment of gastroesophageal reflux disease (GERD) and healing of erosive reflux esophagitis, including prevention of esophagitis relapse. In addition, NEXIUM is indicated in combination with an appropriate antibacterial therapeutic regimen for the eradication of *Helicobacter pylori* infection in patients with duodenal ulcer disease and for the risk reduction of nonsteroidal anti-inflammatory drug (NSAID)-associated gastric ulcer. The current application is for the oral suspension, to be used as an alternative to the capsule formulation for all currently approved indications of esomeprazole.

The rationale for the pellet-based sachet formulation is to provide esomeprazole to patients who have difficulty swallowing a capsule. In this group are patients with esophageal structural anomalies, esophageal dysmotility and dysphasia, geriatric patients, or those who receive nutrition and medication through feeding tubes.

The sponsor has submitted one study (D9612C00032) in support of the current application. Study D9612C00032 is an open-label, randomized, 3-way crossover design that enrolled 96 healthy subjects, 20 to 50 years of age. The aim of the study was to show bioequivalence between the approved oral formulations and the pellet-based sachet.

1.3.2 Efficacy

Although not an efficacy study, the data submitted by the sponsor demonstrate bioequivalence between the pellet-based sachet formulation and the tablet and capsule formulations. Efficacy can be extrapolated by virtue of bioequivalence with products already found to have efficacy.

1.3.3 Safety

All 3 formulations {delayed-release suspension, tablet, delayed-release capsule} of esomeprazole were well tolerated in this study. There were no findings that raised safety concerns. No trends of clinical importance were found regarding AEs in relation to the different formulations of investigational product. There were no pregnancies, no serious adverse events (SAEs), and no discontinuations of investigational product due to adverse events. No subject had a significant laboratory abnormality.

Medical Officer's Comments:

The safety data submitted for this Phase I bioequivalence study did not raise new safety issues.

1.3.4 Dosing Regimen and Administration

Single oral doses of the investigational products were given on 3 study days, separated by wash-out periods of at least 6 days. The following products were given.

Table 1
NDA 21-957

Details of investigational products	
Investigational Product	Dosage form and strength
Esomeprazole	Pellets based sachet formulation, 40 mg
Esomeprazole(as NEXIUM)	Tablet 40 mg
Esomeprazole(as NEXIUM)	Capsule 40 mg

The delayed-release tablet is available in all 105 countries in which esomeprazole is marketed except the United States, where only the delayed-release capsule is available. A single 40mg dose was chosen based on the FDA guidance regarding bioavailability and bioequivalence

studies for orally administered drug products (“Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations”).

1.3.5 Drug-Drug Interactions

No new drug interactions were noted in this study. The current labeling provides details concerning drug interactions and notes extensive metabolism in the liver by CYP2C9 and CYP3A4.

1.3.6 Special Populations

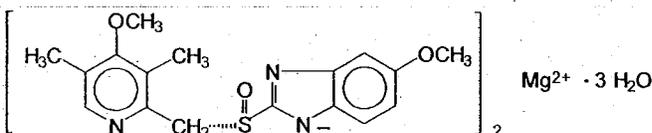
The current labeling for esomeprazole indicates no dosage adjustment based on age or gender is necessary. Additionally, no dosage adjustment is recommended for patients with mild to moderate hepatic insufficiency, nor are the pharmacokinetics of esomeprazole in patients with renal impairment altered relative to those without renal impairment.

APPEARS THIS WAY ON ORIGINAL

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Trade Name (established name): Nexium™ (esomeprazole magnesium)



Proposed Indication: Acute healing and maintenance of erosive esophagitis, and symptomatic Gastroesophageal Reflux Disease, risk reduction of NSAID-Associated Gastric Ulcer

Proposed Age Group: The same as that for which esomeprazole delayed-release capsules are approved.

Pharmacologic Class: Proton Pump Inhibitor

Active Ingredient: bis(5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-yl) magnesium trihydrate inhibits

Route of Administration, description, and Formulation: Delayed-Release Granules Oral Suspension

Proposed Treatment Regimen: 20mg or 40 mg daily

2.2 Currently Available Treatment for Indications

Esomeprazole has been on the market as NEXIUM® Delayed-Release Capsules since March 2000, and is now approved in 105 countries world-wide. Other proton pump inhibitors include rabeprazole, omeprazole, lansoprazole and pantoprazole. Omeprazole is currently available as an oral suspension under the trade name ZEGERID®. Zegerid powder for oral suspension is indicated for short-term treatment of active duodenal ulcer; for short-term treatment of active benign gastric ulcer; for heartburn and other symptoms associated with gastroesophageal reflux disease (GERD); for the short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy; for maintenance of healing of erosive esophagitis (controlled studies do not extend beyond 12 months); and for reduction of risk of upper gastrointestinal bleeding in critically ill patients. The makers of esomeprazole pellet-based sachet propose the following indications for their product: acute healing and maintenance of erosive esophagitis, symptomatic

Gastroesophageal Reflux Disease, and risk reduction of NSAID-associated gastric ulcer. These are the same indications for which Nexium delayed-release granules has been approved.

2.3 Availability of Proposed Active Ingredient in the United States

Esomeprazole delayed-release capsules are marketed in the United States.

2.4 Important Issues With Pharmacologically Related Products

There are no important issues with pharmacologically related products.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

A separate review will be submitted by Dr. Milton Sloan, CMC reviewer.

3.2 Animal Pharmacology/Toxicology

No additional animal Pharmacology/Toxicology data have been submitted for this efficacy supplement. The animal studies have been reviewed as part of the original NDA, and are available for reference in the review by Dr. Ke Zhang.

3.3 Data Sources, Review Strategy, and Data Integrity

3.4 Sources of Clinical Data

Study D9612C00032, "A Single-Centre, Open, Randomized, Three-way Crossover Bioequivalence Study Comparing a Pellets Based Sachet Formulation of Esomeprazole with a Commercial Tablet and a Commercial Capsule of Esomeprazole 40 mg following a Single Oral Dose under Fasting Conditions in Healthy Male and Female Subjects". This Phase I study was conducted at a single-center in Quintiles AB, Sweden. The principal investigator was Jan Vouis, MD.

3.5 Compliance with Good Clinical Practices

According to the sponsor, the clinical study was conducted according to Good Clinical Practice (GCP) guidelines, as documented in the International Conference on Harmonization (ICH) and the Food and Drug Administration (FDA).

3.6 Financial Disclosures

The sponsor has submitted FDA Form 3454 certifying that no investigator of any of the covered clinical studies had any financial interests to disclose.

Medical Officer Comment:

AstraZeneca certified that they did not enter into any financial agreement with the clinical investigators whereby the value of their compensation could be affected by the outcome of the studies.

4 CLINICAL PHARMACOLOGY

4.1 Pharmacokinetics

The estimated geometric means of AUC, C_{max}, and AUC_t were similar for the 40 mg sachet formulation (delayed release suspension), tablet, and capsule of esomeprazole, and were approximately 6 µmol*h/L, 3 µmol/L, and 6 µmol*h/L, respectively.

Table 2
NDA 21-957
Estimated Geometric Means of the PK Variables in healthy male and female subjects

Variable	Treatment	N	Estimate
AUC (µmol*h/L)	Sachet	94	5.85
	Capsule	94	5.97
C _{max} (µmol/L)	Sachet	94	2.84
	Capsule	94	3.16
AUC _t (µmol*h/L)	Sachet	94	5.73
	Capsule	94	5.85

5 INTEGRATED REVIEW OF EFFICACY

Since this was a Phase I bioequivalence study, an efficacy analysis was not done

5.1 Indication

The makers of esomeprazole pellet-based sachet propose the following indications for their product: acute healing and maintenance of erosive esophagitis, symptomatic Gastroesophageal Reflux Disease, and risk reduction of NSAID-associated gastric ulcer.

5.1.1 General Discussion of Endpoints

Primary Objective:

The primary objective of this study was to investigate whether a pellets based sachet formulation of esomeprazole was bioequivalent to the tablet and capsule form following single oral doses of 40 mg. Assessment was made by analysis of two pharmacokinetic parameters: the total area under the plasma concentration versus time curve (AUC) and the observed maximum plasma concentration (C_{max}).

Secondary Objectives:

- To evaluate the pharmacokinetic properties of a new pellets based sachet formulation of esomeprazole, a commercial tablet, and a commercial capsule of esomeprazole following single oral doses of 40 mg, respectively, by assessment of the area under the plasma concentration versus time curve up to the last quantifiable concentration (AUC_t), the time of observed maximum plasma concentration (t_{max}), and the terminal half-life ($t_{1/2}$).
- To evaluate the safety and tolerability of treatment with single doses of a pellets based sachet formulation of esomeprazole in relation to a commercial tablet and a commercial capsule of esomeprazole by assessment of adverse events (AEs) and laboratory variables.

Medical Officer's Comments:

The study objectives relate to bioequivalence, pharmacokinetics and safety. Through a demonstration of bioequivalence to the approved formulations, efficacy can be inferred.

5.1.2 Study Design

The study was conducted as a single-center, open-label, randomized, 3-way crossover bioequivalence study in which healthy male and female volunteers received a single 40 mg dose of esomeprazole, either as a pellets based sachet formulation, a commercial capsule, or a commercial tablet, under fasting conditions.

A total of 96 healthy male and female subjects, aged between 20 and 50 years inclusively, with approximately 50% of each sex, were included in the study in order to have at least 88 evaluable healthy subjects completing the study.

Single oral doses of esomeprazole 40 mg were given either as a tablet, a capsule, or a pellets based sachet formulation on 3 study days, separated by wash-out periods of at least 6 days. Wash-out was 6 days to ensure that no carry-over effect was present. The follow-up visit took

place 5 to 7 days after the last study day because the pregnancy test had the sensitivity to detect a pregnancy after this period of time.

As per the sponsor, the study was done in healthy subjects in order to aid compliance with complex study procedures and to avoid interference with the study results from disease processes and other drugs. The inclusion and exclusion criteria were chosen in order to select subjects who were known to be free from any significant illness relevant to the proposed study.

The inclusion and exclusion criteria are listed below.

Inclusion criteria:

For inclusion in the study, subjects had to fulfill all of the following criteria:

- Provision of informed consent
- Age 20 to 50 years
- Body mass index (BMI=weight/height²) 19 to 27 kg/m²
- Weight 50 to 95 kg
- Clinically normal physical findings and laboratory values, as judged by the investigator.

Exclusion criteria:

Any of the following was regarded as a reason for exclusion from the study:

- Significant clinical illness within the 2 weeks preceding the first dose of investigational products, as judged by the investigator
- History of mental, cardiac, renal, hepatic, neurological, or significant gastrointestinal disease, as judged by the investigator
- History of or ongoing severe allergic disease, as judged by the investigator
- Condition which could modify the absorption of the investigational products, as judged by the investigator
- Pregnancy, planned pregnancy, or lactation
- Childbearing potential, unless judged by the investigator that there was an understanding of the importance of avoiding a pregnancy and of taking the necessary precautions against that (it was permitted to use intrauterine device, implantable progesterone device, or oral contraceptive).
- Use of prescribed medication during the 2 weeks before the first dose of the investigational products and during the study and use of over-the-counter (OTC)
- Drugs (including herbals, vitamins, and minerals) during the week before the first dose of the investigational product and during the study
- Need for concomitant medication except for contraceptives, nasal spray for nasal congestion, and paracetamol for temporary pain relief
- Administration of any investigational drug within the 8 weeks preceding the first dose of the investigational products
- Blood donation within the 12 weeks preceding the first dose of the investigational products and during the entire study

- History of or suspected current drug addiction and/or alcohol abuse
- Moderate to heavy smoking or other sort of nicotine use (>10 cigarettes per day or corresponding amount of nicotine)
- Use of anabolic steroids
- Involvement in the planning and conduct of the study (applied to both AstraZeneca staff and staff at the investigational site)
- Positive test in the drug screen
- Previous randomization to treatment in the present study

Medical Officer's Comments:

Inclusion and Exclusion criterion were acceptable for this Phase I PK and safety study.

5.1.3 Efficacy Findings

As noted, Study D9612C00032 was a bioequivalence study, with efficacy based on establishing bioequivalence between the new pellets based sachet formulation and the already approved tablet and delayed-release granules.

5.1.4 Efficacy Conclusions

No specific efficacy conclusions were drawn from this study.

The 90% CI for the ratios (sachet/capsule and sachet/tablet) of the geometric means for AUC and C_{max} were contained in the interval 0.80 to 1.25, and thus the pellets based sachet formulation of esomeprazole 40 mg is considered to be bioequivalent to the commercial tablet and the commercial capsule of esomeprazole 40 mg. The 90% CI for the ratios (sachet/capsule and sachet/tablet) of the geometric means for AUC_t were also within the stated criterion for bioequivalence. The pharmacokinetic variables t_{1/2} and t_{max} were similar for the 3 different formulations.

Table 3
NDA21-957

Ratios of geometric means and 90% CIs for AUC, C_{max} and AUC_t following single oral doses of esomeprazole 40 mg in healthy male and female subjects under fasting conditions

Variable	Treatment	N	GMR	90% CI	
				Lower	Upper
AUC(μmol*h/L)	Sachet/Capsule	94	0.98	0.93	1.03
C _{max} (μmol/L)	Sachet/Capsule	94	0.90	0.84	0.96
AUC _t (μmol*h/L)	Sachet/Capsule	94	0.98	0.93	1.03

6 INTEGRATED REVIEW OF SAFETY

6.1 Methods and Findings

Findings of safety and tolerability of esomeprazole pellets were derived from one clinical study. There were no serious adverse events, discontinuations due to adverse events, or significant adverse events.

6.2 Deaths

There were no deaths in this study.

6.2.1 Other Serious Adverse Events

No serious adverse events were noted.

6.2.2 Dropouts and Other Significant Adverse Events

No patients withdrew from the study.

6.2.3 Common Adverse Events

The most common adverse events were headache, pharyngitis, nausea, and rhinitis. Adverse events were spread out evenly among all three treatment arms.

6.2.3.1 Eliciting adverse events data in the development program

Information about adverse events was collected from the first administration of the investigational product until the last study day. Serious adverse events were collected during the entire study. Causality was determined by the investigator and recorded with all AE information. All AE were followed up on as long as medically indicated.

The following study flow chart lists the schedule of PK and safety assessments.

Table 4
 NDA 21-957
 Study Flow Chart

Visit no.	1	2	3	4	5
	pre-entry	A/B/C	A/B/C	A/B/C	follow-up
	≤14 days	w-o ^a	w-o	5-7 days	
Study day		1	2	3	
Subject demography	X				
Eligibility criteria	X	X			
Informed consent	X				
Medical history	x				
Physical Exam	X				
Weight,height,BP	X				
ECG, HR	X				
Laboratory screen	X				
Drug screen ^b	X				
Pregnancy Test	X	X	X	X	X
Randomization		X			
Administration of Investigational drugs		X	X	X	
Blood sampling		X	X	X	
AEs		←-----→			

^aw-o; wash-out period; at least 6 days

^bcarried out at pre-entry and once randomly during the study

Medical Officers Comments:

The schedule of assessments is appropriate for this study.

6.2.3.2 Common adverse event tables

Table 5
 NDA 21-957

System Organ Class	Number of subjects with any adverse event (AE)		
	Esomeprazole sachet 40 mg (n=96)	Esomeprazole tablet 40 mg (n=96)	Esomeprazole capsule 40 mg (n=96)
# subjects with AE	26	31	30
Headache	10	11	15
Rhinitis	8	12	6
Pharyngitis	2	1	4
Nausea	2	3	2
Syncope vasovagal	2	2	1
Upper Abdominal Pain	0	1	4
Abdominal Pain	1	2	1
Dyspepsia	1	1	0

Derived from Table 14, NDA21-957

Medical Officer's Comment:

Five syncopal episodes were reported. All but one were in relation to blood sampling, and were characterized as vasovagal. No significant trends were noted.

6.2.4 Laboratory Findings

Blood and urine samples were taken at the pre-entry visit and at the follow-up visit. Among the laboratory safety values recorded were CBC (complete blood count), liver function studies, and urinalysis. No subject had a significant laboratory abnormality.

6.2.5 Vital Signs

The blood pressure and heart rate were measured at the pre-entry visit. No further vital signs are provided in the study report. The sponsor notes no trends of clinical importance.

6.2.6 Electrocardiograms (ECGs)

A 12-lead ECG recording, including measurement of HR, was done at the pre-entry visit. No trends of clinical importance were found. No further ECG recording was done.

6.3 Adequacy of Patient Exposure and Safety Assessments

6.3.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

A total number of 96 healthy subjects, 56 females and 40 males, were randomized to treatment with 40 mg oral esomeprazole, given as a pellets based sachet formulation, a tablet, and a capsule in 3 single doses. The safety population consisted of subjects who received at least 1 dose of investigational product and for whom post-dose data is available. All randomized subjects were given all 3 formulations of investigational products according to the protocol.

6.3.2 Study type and design/patient enumeration

The study was conducted as a single-center, open-label, randomized, 3-way crossover bioequivalence study in which healthy male and female volunteers received single doses of esomeprazole 40 mg, either as a pellets based sachet formulation, a commercial capsule, or a commercial tablet, under fasting conditions.

6.3.2.1 Demographics

Ninety-six (96) subjects (40 males and 56 females) were planned for and randomized into the study. All 96 subjects completed the study. The following table gives a brief summary of baseline characteristics of the safety population.

Summary of baseline characteristics, safety population				
Statistic	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m ²)
Mean	24.9	173.7	68.9	22.8
SD	5.6	7.6	9.3	2.1
Min	20.0	156.0	54.0	19.3
Median	24.0	173.0	68.0	22.3
Max	50.0	195.0	92.0	26.9

6.3.2.2 Extent of exposure (dose/duration)

A total number of 96 healthy subjects, 56 females and 40 males, were randomized to treatment with 40 mg oral esomeprazole, given as a pellets based sachet formulation, a tablet, and a capsule in 3 single doses. The safety population consisted of subjects who received at least 1 dose of investigational product and for whom post-dose data are available. All randomized subjects were given all 3 formulations of investigational products according to the protocol.

6.4 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

There were no significant or new drug-related adverse events found among the healthy subjects enrolled in this study.

7 ADDITIONAL CLINICAL ISSUES

7.1 Dosing Regimen and Administration

The sachet formulation consists of the same enteric-coated pellets of esomeprazole as the capsule formulation. Besides these acid-stabile pellets, the sachet formulation contains inactive excipient granules.

8 OVERALL ASSESSMENT

8.1 Conclusions

All 3 formulations of esomeprazole {pellet-based sachet, tablet, delayed-release capsule} were well tolerated in this study. There were no findings that raised new safety concerns. No trends of clinical importance were found regarding AEs in relation to the different formulations of investigational product. There were no pregnancies, no SAEs and no discontinuations of investigational product due to AEs. No subject had a significant laboratory abnormality.

8.2 Recommendation on Regulatory Action

Approval of the pellet-based sachet formulation of esomeprazole is recommended.

8.3 Labeling Review

From the standpoint of the Clinical/Medical review, the sponsor's proposed labeling changes are acceptable. These changes consist of dosing and pharmacokinetic data, and are addressed in the Clinical Pharmacology Review.

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Nancy Snow
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MEDICAL OFFICER

Hugo Gallo Torres
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MEDICAL OFFICER
